

**REMARKS**

Claims 1-4 are pending in the present application. Claims 5-13 have been cancelled without prejudice to or disclaimer of the subject matter contained therein.

Claim 1 has been amended and claims 5-13 have been cancelled for the sole reason of advancing prosecution. Applicants, by canceling or amending claims herein, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 1 has been amended to recite "a transdermal formulation for external application comprising between about 0.1% to about 10% by weight of a non-steroidal anti-inflammatory analgesic, between about 0.001% to about 0.2% by weight of an alkyl ester of gallic acid, and between about 0.01% to about 10% by weight of a phenolic radical scavenger having a branched-chain lower alkyl group." Support for claim 1 as amended can be found throughout the specification and claims as originally filed, for example paragraphs [0015] and [0017] on pages 6 and 7, paragraph [0019] on pages 7 and 8, and paragraph [0022] on pages 9 and 10 of the present specification. No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

- I. ***At pages 2-5 of the Official Action, claims 1-4 have been rejected under 35 U.S.C. §103(a) over Bertrand et al. (FR 2804024; English language Derwent abstract) in view of Swingle et al., "Anti-Inflammatory Activity of Antioxidants," Anti-inflammatory and anti-rheumatic drugs, pp. 105-126, vol. III (1985).***

The Examiner asserts that it would have been obvious to combine the anti-inflammatory compositions for the treatment of inflammation as described by Bertrand et al. and Swingle et al. to arrive at the presently claimed subject matter.

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U. S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. at 417). Second, the proposed

modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Further, the Supreme Court in *KSR* reiterated the framework for determining obviousness that was stated in *Graham v. John Deere Co.* 383 U.S. 1, 148 USPQ 459 (1966). The four factual inquiries that were recited in *Graham* are as follows: (1) Determining the scope and contents of the prior art; (2) Ascertaining the differences between the prior art and the claims in issue; (3) Resolving the level of ordinary skill in the pertinent art; and (4) Evaluating evidence of secondary considerations, such as unexpected results. *Id.* As stated in **MPEP 2141**, secondary considerations such as unexpected results must be considered in every case in which they are present.

As described in **MPEP § 716.02(a)**, "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). *In Corkhill*, the claimed combination showed an additive result when a diminished result would have been expected. This result was persuasive of nonobviousness even though the result was equal to that of one component alone. Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v.*

*Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners). See **MPEP § 716.02(a) I.**

Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut prima facie obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification

indicated the claimed compound was an average performer on crops other than corn and soybean.). See also *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut prima facie obviousness even though there was no evidence that the compound was effective against all bacteria). See **MPEP § 716.02(a)**

## II.

It is submitted that a proper case of *prima facie* obviousness has not been established because, whether taken alone or together, none of the cited references teach or suggest all the limitations of the claims as required by *In re Wilson*. However, assuming *arguendo*, that each of the elements were taught or suggested by the cited references, Applicants respectfully submit that the formulations of the presently claimed subject matter exhibit unexpectedly superior results.

Amended claim 1 is directed to a transdermal formulation for external application comprising between about 0.1% to about 10% by weight of a non-steroidal anti-inflammatory analgesic (ketoprofen, as elected), between about 0.001% to about 0.2% by weight of an alkyl ester of gallic acid (propyl gallate, as elected), and between about 0.01% to about 10% by weight of a phenolic radical scavenger having a branched-chain lower alkyl group (di-tert-butylhydroxytoluene, i.e. BHT, as elected).

Each of claims 2-4 directly depend from claim 1. Claim 2 recites that the phenolic radical scavenger is at least one selected from the group consisting of BHT, BHA and thymol. Claim 3 recites that the alkyl ester of gallic acid is an ester of gallic

acid and lower alcohol. Claim 4 recites the non-steroidal anti-inflammatory analgesic is at least one selected from the group consisting of ketoprofen, tiaprofen, suprofen, tolmetin, carprofen, benoxaprofen, piroxicam, benzydamine, naproxen, diclofenac, ibuprofen, diflunisal and azapropazone.

In contrast, Bertrand et al. describe a pharmaceutical composition for application to the skin or mucosa, comprising at least one non-steroidal anti-inflammatory as an active agent; at least one ultraviolet radiation filter; and at least one inert excipient or carrier. See Bertrand et al. at the Abstract. Nowhere do Bertrand et al. teach or suggest a transdermal formulation for external application comprising between about 0.1% to about 10% by weight of a non-steroidal anti-inflammatory analgesic, between about 0.001% to about 0.2% by weight of an alkyl ester of gallic acid, and between about 0.01% to about 10% by weight of a phenolic radical scavenger having a branched-chain lower alkyl group, as presently claimed.

In further contrast, Swingle et al. describe that antioxidant compounds possess anti-inflammatory activity. According to Swingle et al., BHA, BHT, propyl gallate, DPPD and ethoxyquin are antioxidants that have some bioavailability. See Swingle et al. at pages 13 and 14, Section IV. Nowhere do Swingle et al. teach or suggest a transdermal formulation for external application comprising between about 0.1% to about 10% by weight of a non-steroidal anti-inflammatory analgesic, between about 0.001% to about 0.2% by weight of an alkyl ester of gallic acid, and between about 0.01% to about 10% by weight of a phenolic radical scavenger having a branched-chain

lower alkyl group, as presently claimed. Accordingly, Applicants respectfully submit that a proper case of *prima facie* obviousness has not been established because, whether taken alone or in combination, none of Bertrand et al. and Swingle et al. teach or suggest all the limitations of the claims, as required by *In re Wilson*.

Additionally, assuming *arguendo* that each and every element were taught by the cited references, Applicants respectfully submit that the presently claimed pharmaceutical formulations exhibited unexpectedly superior reduction in phototoxicity through the synergistic action of combining an alkyl ester of gallic acid and BHT.

In this regard, Applicants respectfully draw the Examiner's attention to Tables 1-3, on pages 21 and 23 of the present specification. Tables 1-3 show the results of *in vitro* phototoxicity experiments using formulations according to the presently claimed subject matter compared to formulations comprising ketoprofen alone. Applicants note that the transdermal formulations comprising an alkyl ester of gallic acid, a phenolic radical scavenger having a branched-chain lower alkyl group, and a non-steroidal anti-inflammatory analgesic, as presently claimed, exhibited an unexpectedly superior reduction in phototoxicity as compared to formulations lacking one or more of the claimed components. Further, Applicants draw the Examiner's attention to Tables 4 and 5, on page 23 of the present specification. Tables 4 and 5 show the results of *in vivo* photosensitivity experiments using formulations according to the presently claimed subject matter compared to formulations comprising ketoprofen alone. Applicants note that the presently claimed transdermal formulations comprising a combination of an

alkyl ester of gallic acid, a phenolic radical scavenger having a branched-chain lower alkyl group, and a non-steroidal anti-inflammatory analgesic, exhibited an unexpectedly superior reduction in photosensitivity as compared to formulations lacking the presently claimed combination.

Applicants submit that these results demonstrate that the methods according to the presently claimed subject matter exhibited unexpectedly superior results in view of the cited references. Accordingly, Applicants respectfully submit that nothing in Bertrand et al., and Swingle et al., taken alone or together, render the present claims obvious within the meaning of 35 USC § 103. Thus, the Examiner is respectfully requested to reconsider and withdraw this rejection

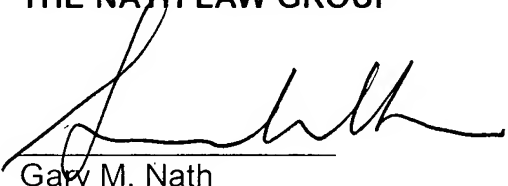


**CONCLUSION**

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,  
**THE NATH LAW GROUP**

A handwritten signature in black ink, appearing to read 'Gary M. Nath', written over a horizontal line.

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